N-terminal pro-brain natriuretic peptide (NT-proBNP) predicts the cardio-renal response to aliskiren in patients with type 2 diabetes at high renal and cardiovascular risk

Idzerda, Nienke M. A.; Persson, Frederik; Pena, Michelle J.; Brenner, Barry M.; Brunel, Patrick; Chaturvedi, Nish; McMurray, John J.; Parving, Hans-Henrik; de Zeeuw, Dick; Heerspink, Hiddo J. L.

Published in:
Diabetes obesity & metabolism

DOI:
10.1111/dom.13465

Publication date:
2018

Received: 6 June 2018 | Revised: 29 June 2018 | Accepted: 5 July 2018

DOI: 10.1111/dom.13465

WILEY

BRIEF REPORT

N-terminal pro-brain natriuretic peptide (NT-proBNP) predicts the cardio-renal response to aliskiren in patients with type 2 diabetes at high renal and cardiovascular risk

Nienke M. A. Idzerda MD[1] | Frederik Persson PhD[2] | Michelle J. Pena PhD[1] | Barry M. Brenner PhD[3] | Patrick Brunel MD[4] | Nish Chaturvedi PhD[5] | John J. McMurray PhD[6] | Hans-Henrik Parving PhD[7] | Dick de Zeeuw PhD[1] | Hiddo J. L. Heerspink PhD[1]

[1]Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands

[2]Steno Diabetes Centre Copenhagen, Copenhagen, Denmark

[3]Cardiovascular Division, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

[4]Novartis, Pharma AG, Basel, Switzerland

[5]Institute of Cardiovascular Sciences, University College London, London, UK

[6]BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, UK

[7]Department of Medical Endocrinology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Correspondence
Hiddo J. L. Heerspink PhD, Hanzeplein 1, PO Box 30001, 9700 RB Groningen, The Netherlands.
Email: h.j.lambers.heerspink@umcg.nl

Funding information
Innovative Medicines Initiative, Grant/Award Number: 115974; Nederlandse Organisatie voor Wetenschappelijk Onderzoek, Grant/Award Number: 917.15.306; Novartis; Novo Nordisk, Grant/Award Number: NNF14SA0003

Sodium retention and volume overload are the main determinants of poor response to renin-angiotensin-aldosterone system (RAAS) inhibition in patients with diabetes. As volume excess can exist without symptoms, biomarkers are needed to identify a priori which patients are volume overloaded and may experience less benefit from RAAS inhibition. N-terminal pro-brain natriuretic peptide (NT-proBNP) is released in the setting of increased cardiac wall stress and volume overload. We conducted a post hoc analysis among 5081 patients with type 2 diabetes mellitus participating in the ALTITUDE trial to investigate whether NTproBNP can predict the effects of additional therapy with aliskiren on cardio-renal endpoints. Aliskiren compared to placebo reduced the risk of the primary cardio-renal endpoint events by 20% (95% confidence interval [CI] 16 to 61) and 2% (95% CI −42 to 30) in the two lowest NT-proBNP tertiles, and it increased the risk by 25% (95% CI −4 to 96) in the highest NT-proBNP tertile (*P* value for trend = 0.009). Similar trends were observed for the cardiovascular and end-stage renal disease endpoints. Effects of aliskiren compared to placebo on safety outcomes (hyperkalaemia and hospitalization for acute kidney injury) were independent of NT-proBNP. In conclusion, baseline NT-proBNP may be used as a marker to predict the response to aliskiren with regard to cardio-renal outcomes when added to standard therapy with RAAS inhibition.

KEYWORDS

cardiovascular disease, clinical trial, diabetes complications, type 2 diabetes

1 | INTRODUCTION

The antihypertensive and anti-albuminuric response to renin-angiotensin-aldosterone system (RAAS) therapy varies considerably among people with type 2 diabetes.[1,2] People with type 2 diabetes are susceptible to retaining sodium and fluid as a result of disturbed insulin homeostasis.[3] Previous studies have shown that sodium retention and subsequent volume overload are the main determinants of poor response to RAAS therapy.[4,5] Accordingly, volume restriction by means of co-diuretic treatment or a low sodium diet enhances the blood pressure-lowering and albuminuria-reducing effects of RAAS inhibition.[6] Diuretic treatment is therefore recommended, although not always implemented in clinical practice. As volume excess can exist without symptoms, it is difficult to identify

a priori which patients are volume overloaded and will have a less beneficial response to RAAS inhibition; therefore, biomarkers that represent volume status and response to RAAS inhibition are desired.

N-terminal pro-brain natriuretic peptide (NT-proBNP) is secreted from the ventricular myocardium in response to increased myocyte stress and volume overload.[7] This suggests that high levels of NT-proBNP may be a marker of excess volume overload in patients without overt heart failure and may be an indicator of response to RAAS intervention.

To test this hypothesis, we performed a post hoc analysis of the ALTITUDE trial in which patients with type 2 diabetes with increased cardiovascular or renal risk were randomly assigned to aliskiren or placebo treatment on top of treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). The aim of the present study was to determine whether NT-proBNP predicts the response to aliskiren on cardio-renal endpoints.

2 | MATERIALS AND METHODS

2.1 | Participants and study design

The ALTITUDE trial was a randomized, double-blind, placebo-controlled trial conducted at 854 centres in 36 countries. The study design and principal findings have been published previously.[8] In short, 8561 people with type 2 diabetes mellitus at high risk of cardiovascular and renal events were assigned to either aliskiren 300 mg/d or matched placebo in addition to antihypertensive therapy consisting of an individually titrated optimal recommended dose of ACE inhibitor or ARB, but not both. Randomized participants were followed for a median of 32.9 months for occurrence of cardiovascular and renal events. Inclusion criteria were: persistent macroalbuminuria (urinary albumin:creatinine ratio [UACR] ≥200 mg/g), an estimated glomerular filtration rate (eGFR) of ≥30 to ≤60 mL/min/1.73 m^2 and persistent microalbuminuria (UACR ≥20 mg/g to ≤200 mg/g), or a history of cardiovascular disease (including heart failure New York Heart Association class I/II) and an eGFR of ≥30 and < 60 mL/min/1.73 m^2. All participants signed informed consent before enrolment, and the study was approved by the local institutional review board of each participating centre.

2.2 | Measurements and outcomes

At each visit, participants submitted three consecutive first morning void samples. Urinary albumin (mg/L) and creatinine (g/L), and thereby UACR, were measured in each first morning void sample by immunoturbidimetry. The geometric mean of UACR was calculated from the three first morning void samples and used for analysis. Serum creatinine concentration was measured by Jaffe reaction (Roche Diagnostics, Risch-Rotkreuz, Switzerland). Blood pressure was measured using an automated validated device, while the patient was in a sitting position. The mean of three blood pressure measurements with 1- to 2-minute intervals was used for analysis. eGFR was calculated with the Modification of Diet in Renal Disease formula.[9] NT-proBNP was measured in plasma at baseline. All laboratory analyses, including first morning void urine analysis, were performed at central laboratories in Europe or the United States.

The primary cardio-renal endpoint was defined as a composite of cardiac arrest with resuscitation, non-fatal myocardial infarction, non-fatal stroke, unplanned hospitalization for heart failure, cardiovascular death, end-stage renal disease (defined as the need for chronic dialysis, renal transplantation or a serum creatinine concentration > 530 μmol/L [6.0 mg/dL] sustained for at least 1 month), doubling of serum creatinine, or death attributable to kidney failure, defined as the need for renal-replacement therapy with no dialysis or transplantation available or initiated. Safety outcomes included acute kidney injury and hyperkalaemia. All endpoints were adjudicated by a central endpoint committee using rigorous definitions.

2.3 | Statistical analysis

The effect of aliskiren compared to placebo on cardio-renal and safety outcomes in tertiles of baseline NT-proBNP as well as for continuous measures of NT-proBNP was estimated from unadjusted Cox proportional hazard regression models. For participants who experienced >1 primary event, survival time to the first renal or cardiovascular event was used in each analysis. Participants who did not have an endpoint of interest during the study were censored at the study cut-off date. Test for trends in treatment effects across NT-proBNP tertiles as categorical and continuous variables were conducted by adding interaction terms (NT-proBNP * treatment assignment) to the relevant Cox models. In an additional analysis, the Cox model was adjusted for age, gender, UACR, eGFR, systolic blood pressure (SBP), diastolic blood pressure, glycated haemoglobin, body mass index, LDL cholesterol, HDL cholesterol, triglycerides, history of cardiovascular disease (yes/no), haemoglobin, potassium, use of diuretics, smoking status (yes/no), and alcohol consumption (yes/no) to assess whether the interaction between baseline NT-proBNP and treatment assignment persisted after accounting for differences in these variables across NT-proBNP tertiles. These covariates were chosen in accordance with previous analyses in this population. To further delineate the relationship between baseline levels of NT-proBNP and the cardio-renal endpoints, a subpopulation treatment effect pattern plot (STEPP) was used to explore patterns of treatment effect for varying levels of baseline NT-proBNP. STEPP enables the calculation of drug estimates along a continuous scale with overlapping participant subgroups.[10,11] An analysis of covariance (ANCOVA) model was used to assess the treatment effect on albuminuria and blood pressure at month 6. Tests for trends in treatment effects were assessed by adding an interaction term to the ANCOVA model.

For continuous variables that are not normally distributed, such as NT-proBNP and UACR, a natural log transformation was applied before analysis to fulfil assumptions for regression analyses. Differences in baseline characteristics across NT-proBNP tertiles were tested using analysis of variance, with Bonferroni adjustments for multiple comparisons for continuous variables. χ^2 tests were used to test for differences in categorical variables.

Two-sided *P* values <0.05 were taken to indicate statistical significance. Data were analysed with SAS version 9.3 (SAS Institute, Cary, North Carolina).

3 | RESULTS

Of the 8561 participants enrolled in the ALTITUDE trial, 5081 (59.5%) had NT-proBNP measurements available and did not have a history of congestive heart failure at baseline. These were included in the analysis. In comparing the characteristics of the overall ALTITUDE population with those in whom NT-proBNP was measured, no relevant differences were observed (Table S1). The baseline characteristics stratified by tertile of baseline NT-proBNP are shown in Table 1. Median NT-proBNP levels in increasing tertiles of NT-proBNP were 50, 157 and 534 ng/L, respectively. Participants in the lower NT-proBNP tertile were younger, had lower SBP, a higher eGFR, were less likely to have a cardiovascular disease history, and less likely to use β-blockers or diuretics (Table 1).

3.1 | Baseline NT-pro BNP predicts effects of aliskiren

The effect of aliskiren compared with placebo on albuminuria and SBP was modified by baseline NT-proBNP level (*P* for interaction albuminuria = 0.004 and *P* for interaction systolic SBP = 0.009). In the aliskiren group, compared with the placebo group, there was a significant reduction in UACR and SBP of 22.2% (95% CI −29.0 to −14.8) and 3.2 mm Hg (95% CI −5.0 to −1.4), respectively, in the lowest NT-proBNP tertile, whereas aliskiren had no effect on these surrogates in the upper NT-proBNP tertile (Figure S1).

The effects of aliskiren on cardio-renal endpoints were also modified by baseline NT-proBNP level (*P* for interaction = 0.009). In the upper NT-proBNP tertile, aliskiren compared with placebo increased the risk of the cardio-renal endpoint (hazard ratio [HR] 1.25 [95% CI 1.04–1.51]), whereas the HRs associated with aliskiren treatment in the middle and lower tertile were 0.96 (95% CI 0.76–1.26) and 0.80

TABLE 1 Baseline characteristics stratified by tertiles of baseline N-terminal pro-brain natriuretic peptide

	Tertile 1		Tertile 2		Tertile 3	
	Placebo	Aliskiren	Placebo	Aliskiren	Placebo	Aliskiren
Number of patients	856	846	860	828	832	859
NT-proBNP, ng/L	50 (2.5, 95)	50 (2.5, 95)	157 (95, 266)	158 (95, 273)	524 (266, 40 500)	544 (266, 40 500)
Age[a], y	59.7 (9.7)	59.9 (9.4)	64.7 (9.2)	65.1 (9.0)	67.5 (9.1)	67.2 (9.1)
Gender[a], *n* (%)						
Men	623 (72.8)	610 (72.1)	566 (65.8)	545 (65.8)	574 (69.0)	586 (68.2)
Women	233 (27.2)	236 (27.9)	294 (34.2)	283 (34.2)	258 (31.0)	273 (31.8)
Race[a], *n* (%)						
White	364 (43.0)	379 (45.2)	469 (54.2)	436 (52.5)	498 (59.5)	518 (60.0)
Black	31 (3.7)	22 (2.6)	19 (2.2)	16 (1.9)	17 (2.0)	7 (0.8)
Hispanic	409 (48.3)	382 (45.5)	333 (38.5)	327 (39.4)	254 (30.3)	280 (32.4)
Other	42 (4.9)	56 (6.6)	44 (5.1)	52 (6.2)	68 (8.1)	58 (6.7)
SBP[a], mm Hg	133.3 (15.2)	133.0 (14.7)	137.8 (16.2)	138.1 (15.2)	141.6 (17.0)	140.9 (17.0)
DBP[a], mm Hg	76.0 (8.8)	76.3 (8.7)	73.8 (9.5)	73.7 (9.2)	73.5 (10.6)	73.3 (10.7)
Body mass index, kg/m^2	29.5 (5.9)	29.6 (5.6)	29.5 (5.7)	29.7 (5.9)	29.2 (5.7)	29.2 (5.8)
Haemoglobin[a], g/L	137 (16)	136 (16)	130 (17)	131 (17)	127 (18)	127 (18)
HbA1c[a], mmol/mol	62 (13)	63 (13)	61 (13)	61 (12)	60 (12)	60 (12)
HDL cholesterol[a], (mmol/L)	1.18 (0.30)	1.17 (0.31)	1.21 (0.35)	1.21 (0.32)	1.22 (0.34)	1.20 (0.35)
LDL cholesterol[a], (mmol/L)	2.64 (0.94)	2.60 (0.92)	2.53 (1.00)	2.58 (0.95)	2.50 (0.96)	2.53 (1.00)
Triglycerides[a], (mmol/L)	5.68 (4.48)	5.69 (4.99)	4.82 (3.35)	4.75 (2.86)	4.28 (2.55)	4.55 (3.39)
eGFR[a, b], mL/min/1.73 m^2	67.8 (28.2)	66.4 (27.0)	56.2 (20.0)	56.1 (20.3)	50.4 (17.3)	52.0 (17.8)
UACR[a], mg/g	352 (149, 841)	337 (132, 766)	290 (62, 1006)	314 (60, 891)	326 (55, 1253)	324 (64, 1277)
History of CV disease[a], *n* (%)	175 (20.4)	171 (20.2)	301 (35.0)	280 (33.8)	416 (50.0)	405 (47.1)
Diabetic retinopathy, *n* (%)	315 (37.2)	304 (36.2)	314 (36.3)	336 (40.4)	345 (41.2)	342 (39.6)
Concomitant medication, *n* (%)						
β-blockers[a]	268 (31.3)	263 (31.1)	407 (47.3)	405 (48.9)	504 (60.6)	524 (61.0)
Diuretics[a]	430 (50.2)	431 (50.9)	512 (59.5)	493 (59.5)	560 (67.3)	556 (64.7)
Insulin[a]	485 (56.7)	481 (56.9)	500 (58.1)	496 (59.9)	481 (57.8)	516 (60.1)
Sulphonylureas	265 (31.3)	255 (30.4)	276 (31.9)	255 (30.7)	273 (32.6)	267 (30.9)
Biguanides[a]	426 (50.4)	424 (50.5)	363 (42.0)	362 (41.9)	347 (41.5)	362 (41.9)

Abbreviations: CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; IQR, interquartile range; NT-proBNP, N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure; UACR, urinary albumin:creatinine ratio. Within each tertile, values are stratified for treatment with aliskiren or placebo. Numeric variables are presented as mean (SD) if normally distributed and skewed data were presented as median (IQR). NT-proBNP is presented as median (range). Categorical variables are presented as frequency (%).

[a] Statistically significant between tertiles of NT-proBNP.

[b] Calculated with the Modification of Diet in Renal Disease study equation.

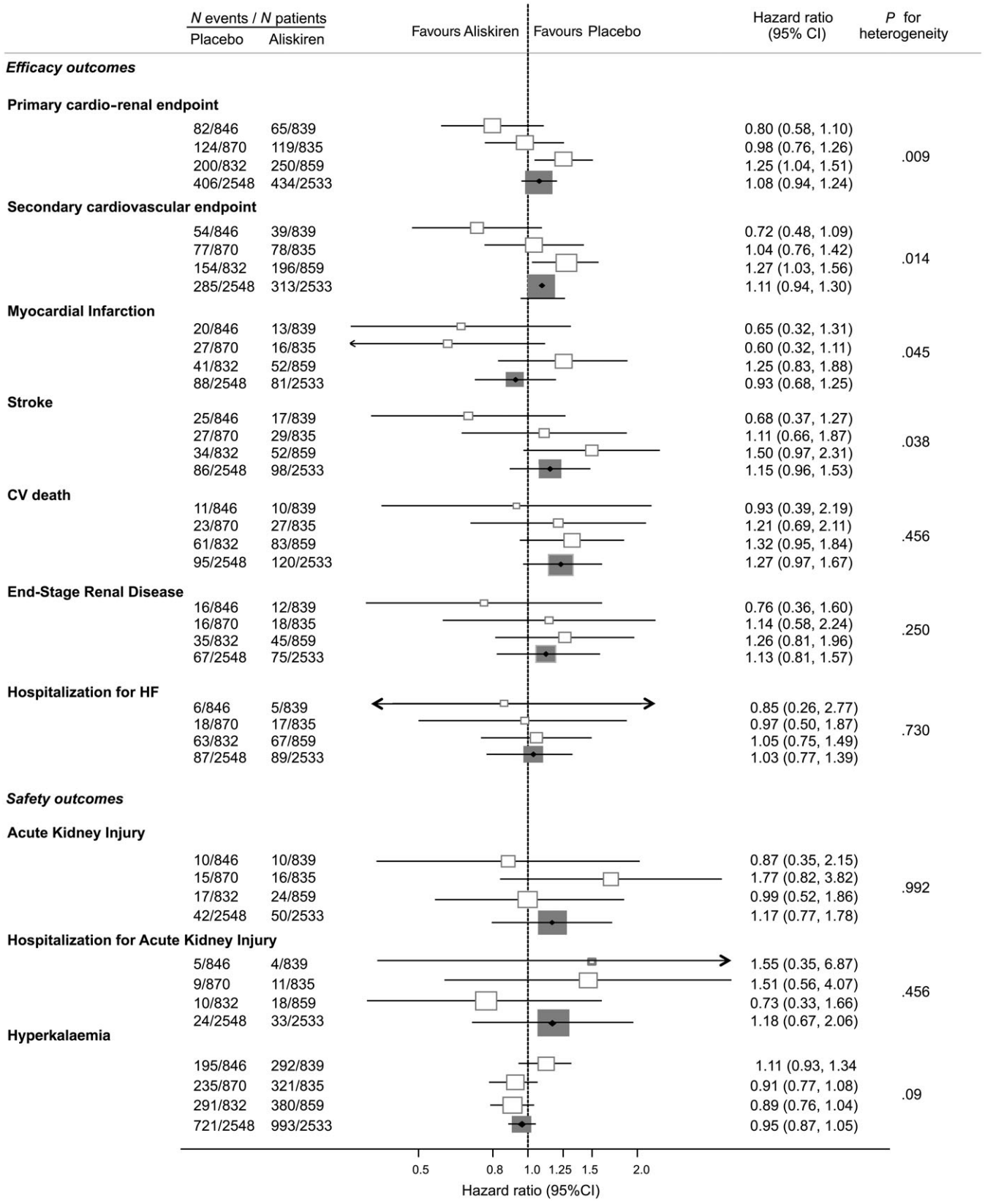

FIGURE 1 Effect of aliskiren vs placebo on cardiovascular (CV) and renal endpoints, and safety outcomes (acute kidney injury, hospitalization for acute kidney injury and hyperkalaemia) according to baseline N-terminal pro-brain natriuretic peptide tertile. Solid boxes represent estimates of treatment effects. The centre of the boxes is placed on the estimate of the treatment effect, the horizontal line represents the width of the 95% confidence interval (CI). The primary cardio-renal endpoint was defined as a composite of cardiac arrest with resuscitation, non-fatal myocardial infarction, non-fatal stroke, unplanned hospitalization for heart failure (HF), CV death, end-stage renal disease (defined as the need for chronic dialysis, renal transplantation or a serum creatinine concentration > 530 μmol/L [6.0 mg/dL] sustained for at least 1 month), doubling of serum creatinine, or death attributable to kidney failure, defined as the need for renal-replacement therapy with no dialysis or transplantation available or initiated. The secondary CV endpoint was defined as a composite of cardiac arrest with resuscitation, non-fatal myocardial infarction, non-fatal stroke, unplanned hospitalization for HF and CV death

(95% CI 0.58–1.10), respectively (Figure 1). A statistically significant trend across NT-proBNP tertiles was also observed for the cardiovascular endpoint, myocardial infarction and stroke. A similar trend was observed for end-stage renal disease and hospitalization for heart failure, although these trends did not reach statistical significance, possibly because of the relatively small number of events. The interaction between aliskiren assignment and NT-proBNP levels persisted (P = 0.005 for the composite cardio-renal endpoint) in a multivariable adjusted model. Additionally, there was no difference in interaction between NT-proBNP and aliskiren between participants with and without diuretic use at baseline (P = 0.48). The STEPP analyses, in which NT-proBNP was defined as a continuous instead of a categorical variable, provided results similar to the main analysis and showed that aliskiren tended to increase the risk of cardiorenal events at higher NT-proBNP levels (Figure S2).

3.2 | Effect of aliskiren vs placebo on safety outcomes according to baseline NT-proBNP levels

The HRs for adverse event rates in the aliskiren group vs placebo according to NT-proBNP tertile are shown in Figure 1. The administration of aliskiren resulted in similar relative effects on hyperkalaemia, acute kidney injury or hospitalization for acute kidney injury, irrespective of baseline NT-proBNP levels.

4 | DISCUSSION

The present study shows that the relative risks for cardiovascular and renal events achieved with the direct renin inhibitor aliskiren as adjunct to RAAS blockade are modified by baseline NT-proBNP levels. At higher NT-proBNP levels, aliskiren compared to placebo increased the risk of the cardio-renal endpoint, while in the lower NT-proBNP tertile, treatment with aliskiren tended to reduce cardio-renal risk. These results suggest that NT-proBNP, a marker of vascular wall stress and fluid overload, can possibly be used to identify patients more likely to respond to dual RAAS inhibition with aliskiren.

Volume overload is frequently observed in patients with type 2 diabetes at high cardio-renal risk.[12,13] Extracellular volume restriction, by means of moderating dietary sodium intake or concomitant diuretic treatment has been shown to improve the albuminuria-reducing and blood pressure-lowering response to RAAS blockade as well as the efficacy of RAAS blockade to decrease cardio-renal risk.[5,14,15] The present study shows that NT-proBNP can help to identify individuals who may not respond to dual RAAS inhibition with aliskiren and who may benefit from diuretic treatment or dietary sodium-lowering. Indeed, it has been shown that hydrochlorothiazide or a low sodium diet is particularly effective in reducing albuminuria and lowering blood pressure in patients with NT-proBNP levels >125 pg/mL who were already receiving a maximum dose of losartan.[16] Whether diuretic treatment or a low sodium diet as adjunct to RAAS blockade will prevent cardio-renal endpoints in patients with high NT-proBNP requires further study.

The primary results of the ALTITUDE trial showed that aliskiren did not confer renal or cardiovascular protection in patients with type 2 diabetes at high risk. We previously showed that patients with a > 30% reduction in albuminuria during the first 6 months of the ALTITUDE trial had a substantially lower cardio-renal risk compared to patients with a modest increase in albuminuria.[17] We now extend these findings and demonstrate that baseline NT-proBNP enables the selection of subgroups of patients who will or will not benefit from aliskiren. We also showed that low and high NT-proBNP levels were independently associated with presence or absence of a reduction in SBP and UACR, while adverse event rates, including hyperkalaemia and acute kidney injury, were similar across NT-proBNP tertiles. Moreover, these results support our previous finding that patients with a lack of reduction in albuminuria were probably volume overloaded and therefore did not respond to aliskiren.

How do the results of our study relate to the current literature? A previous post hoc analysis of the I-PRESERVE trial in patients with heart failure showed that, although NT-proBNP independently predicted all-cause mortality and cardiovascular hospitalizations, the response to ARB therapy was attenuated with higher NT-proBNP levels.[18] Additionally, the efficacy of statins in patients with elevated cardiovascular risk also appears to be higher in patients with lower NT-proBNP levels, although the mechanisms by which statin treatment would be more beneficial in patients with low NT-proBNP are incompletely understood.[19,20] The present study extends these previous findings to a broad population of patients with type 2 diabetes with or without cardiovascular disease and varying levels of kidney function and albuminuria.

The main limitation of this post hoc analysis of the data from ALTITUDE is that sodium intake and diuretic use were not standardized. Indeed during the trial, participants were advised to start diuretic treatment; however, this limitation may have led to an underestimation of the reported interaction between the aliskiren treatment effects and NT-proBNP levels. Secondly, significant differences in baseline characteristics were observed across NT-proBNP tertiles. It is therefore possible that participants in the highest NT-proBNP tertile were sicker and therefore responded poorly to aliskiren, independent of the actual NT-proBNP level; however, in multivariable Cox regression analyses the interaction between aliskiren treatment and NT-proBNP persisted, suggesting that the interaction was independent of other patient and disease characteristics. Nevertheless, we cannot exclude residual confounding, and a prospectively designed clinical trial is required to prove this hypothesis.

In conclusion, NT-proBNP, a marker reflecting volume overload, may predict the effect of the response to aliskiren on surrogate and clinical outcomes when added to conventional therapy with RAAS blockade in patients with type 2 diabetes at high renal or cardiovascular risk.

ACKNOWLEDGMENTS

The ALTITUDE trial was sponsored by Novartis (the authors H.H.P., B.M.B., J.J.V.M., N.C. and D.d.Z. were at that time part of the Steering Committee). We thank all investigators, patients and support staff. We would also like to thank the members of the Steering Committee and the Safety Committee. Funding for this analysis was received from IMI BEAt-DKD program. The BEAt-DKD project has received

funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115974. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation program and EFPIA. This study was also conducted in the framework of the PROTON project (Novo Nordisk Foundation, Grant Number NNF14SA0003). H.J.L.H. is supported by a VIDI grant from the Netherlands Organization for Scientific Research (917.15.306).

Conflict of interest

N.M.A.I. and M.J.P. report no conflicts of interest. F.P. reports having received research grants from AstraZeneca and Novartis and lecture fees from Novartis, Eli Lilly, MSD, AstraZeneca, Sanofi and Boehringer Ingelheim and having served as a consultant for Astra Zeneca, Bayer, Amgen, Novo Nordisk and MSD. D.d.Z. is consultant for and received honoraria (to employer) from AbbVie, Astellas, Eli-Lilly, Chemocentryx, Fresenius, and Janssen. H.H.P. is consultant for and received honoraria from AbbVie, Novartis and Astra Zeneca. H.J.L.H. is consultant for AbbVie, Astellas, Astra Zeneca, Boehringer Ingelheim, Fresenius, Janssen, and Merck and has a policy that all honoraria are paid to his employer. P.B. as an employee of Novartis pharma AG is entitled to receive Novartis stocks and stock options.

Author contributions

N.M.A.I. and H.L.J.H. wrote the manuscript and conducted statistical analysis. M.J.P. contributed to dataset preparation and review of the manuscript. F.P., B.M.B., P.B., N.C., J.J.M. and H.H.P. were involved in data collection and reviewed the manuscript. H.J.L.H. and D.d.Z. defined the analysis plan and edited the manuscript.

ORCID

Nienke M. A. Idzerda http://orcid.org/0000-0001-6912-3429
Michelle J. Pena http://orcid.org/0000-0003-3340-2893
John J. McMurray http://orcid.org/0000-0002-6317-3975
Hiddo J. L. Heerspink http://orcid.org/0000-0002-3126-3730

REFERENCES

1. Eijkelkamp WB, Zhang Z, Remuzzi G, et al. Albuminuria is a target for renoprotective therapy independent from blood pressure in patients with type 2 diabetic nephropathy: post hoc analysis from the reduction of endpoints in NIDDM with the angiotensin II antagonist losartan (RENAAL) trial. *J Am Soc Nephrol*. 2007;18:1540-1546.
2. Hellemons ME, Persson F, Bakker SJ, et al. Initial angiotensin receptor blockade-induced decrease in albuminuria is associated with long-term renal outcome in type 2 diabetic patients with microalbuminuria: a post hoc analysis of the IRMA-2 trial. *Diabetes Care*. 2011;34:2078-2083.
3. Reaven GM. Relationships among insulin resistance, type 2 diabetes, essential hypertension, and cardiovascular disease: similarities and differences. *J Clin Hypertens (Greenwich)*. 2011;13:238-243.
4. Ekinci EI, Thomas G, Thomas D, et al. Effects of salt supplementation on the albuminuric response to telmisartan with or without hydrochlorothiazide therapy in hypertensive patients with type 2 diabetes are modulated by habitual dietary salt intake. *Diabetes Care*. 2009;32:1398-1403.
5. Lambers Heerspink HJ, Holtkamp FA, Parving HH, et al. Moderation of dietary sodium potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers. *Kidney Int*. 2012;82:330-337.
6. Kwakernaak AJ, Krikken JA, Binnenmars SH, et al. Effects of sodium restriction and hydrochlorothiazide on RAAS blockade efficacy in diabetic nephropathy: a randomised clinical trial. *Lancet Diabetes Endocrinol*. 2014;2:385-395.
7. Martinez-Rumayor A, Richards AM, Burnett JC, Januzzi JL Jr. Biology of the natriuretic peptides. *Am J Cardiol*. 2008;101:3-8.
8. Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med*. 2012;367:2204-2213.
9. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. *Ann Intern Med*. 1999;130:461-470.
10. Bonetti M, Gelber RD. A graphical method to assess treatment-covariate interactions using the Cox model on subsets of the data. *Stat Med*. 2000;19:2595-2609.
11. Lazar AA, Cole BF, Bonetti M, Gelber RD. Evaluation of treatment-effect heterogeneity using biomarkers measured on a continuous scale: subpopulation treatment effect pattern plot. *J Clin Oncol*. 2010;28:4539-4544.
12. Mullens W, Verbrugge FH, Nijst P, Tang WH. Renal sodium avidity in heart failure: from pathophysiology to treatment strategies. *Eur Heart J*. 2017;38(24):1872-1882.
13. Wong TC, Piehler KM, Kang IA, et al. Myocardial extracellular volume fraction quantified by cardiovascular magnetic resonance is increased in diabetes and associated with mortality and incident heart failure admission. *Eur Heart J*. 2014;35:657-664.
14. Vogt L, Waanders F, Boomsma F, de Zeeuw D, Navis G. Effects of dietary sodium and hydrochlorothiazide on the antiproteinuric efficacy of losartan. *J Am Soc Nephrol*. 2008;19:999-1007.
15. Slagman MC, Waanders F, Hemmelder MH, et al. Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial. *BMJ*. 2011;343:d4366.
16. Slagman MC, Waanders F, Vogt L, et al. Elevated N-terminal pro-brain natriuretic peptide levels predict an enhanced anti-hypertensive and anti-proteinuric benefit of dietary sodium restriction and diuretics, but not angiotensin receptor blockade, in proteinuric renal patients. *Nephrol Dial Transplant*. 2012;27:983-990.
17. Heerspink HJ, Ninomiya T, Persson F, et al. Is a reduction in albuminuria associated with renal and cardiovascular protection? A post hoc analysis of the ALTITUDE trial. *Diabetes Obes Metab*. 2016;18:169-177.
18. Anand IS, Rector TS, Cleland JG, et al. Prognostic value of baseline plasma amino-terminal pro-brain natriuretic peptide and its interactions with irbesartan treatment effects in patients with heart failure and preserved ejection fraction: findings from the I-PRESERVE trial. *Circ Heart Fail*. 2011;4:569-577.
19. Heart Protection Study Collaborative Group, Emberson JR, Ng LL, et al. N-terminal Pro-B-type natriuretic peptide, vascular disease risk, and cholesterol reduction among 20,536 patients in the MRC/BHF heart protection study. *J Am Coll Cardiol*. 2007;49:311-319.
20. Cleland JG, McMurray JJ, Kjekshus J, et al. Plasma concentration of amino-terminal pro-brain natriuretic peptide in chronic heart failure: prediction of cardiovascular events and interaction with the effects of rosuvastatin: a report from CORONA (Controlled Rosuvastatin multinational trial in heart failure). *J Am Coll Cardiol*. 2009;54:1850-1859.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Idzerda NMA, Persson F, Pena MJ, et al. N-terminal pro-brain natriuretic peptide (NT-proBNP) predicts the cardio-renal response to aliskiren in patients with type 2 diabetes at high renal and cardiovascular risk. *Diabetes Obes Metab*. 2018;20:2899–2904. https://doi.org/10.1111/dom.13465